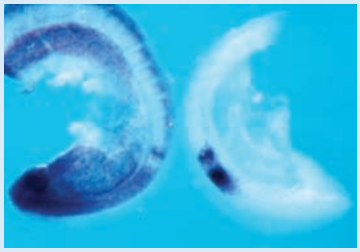
Text By William A. Wells
wellsw@rockefeller.edu

Making stripes

Somites, the precursors of vertebrae, striated muscle, and dermis, are laid down in a timed sequence from anterior to posterior. Now, Alexander Aulehla, Bernhard Herrmann (Max-Planck-Institut für Immunbiologie, Freiburg, Germany), and colleagues report that a gradient and two dueling molecular clocks, all driven directly or indirectly by Wnt3a, combine to create the striped pattern of somites.

The gradient and clock ideas have been proposed before. But, says Herrmann, "what was completely unclear was how the gradient and clock are coupled." That link is now provided by a single protein, Wnt3a, which is connected to both processes.



Herrmann/Elsevier

Axin2 (left) and the Notch pathway (right) oscillate out of phase to create somites.

Wnt3a came into the picture when the group discovered Wnt-dependent Axin2 expression in the tail bud and presomitic mesoderm (PSM). Axin2 expression was cyclic, but oscillated out of phase with the known oscillation of Notch pathway activity, which is also dependent on Wnt3a activity.

Known signaling pathways provide some plausible circuitry. Axin2 produced by Wnt pathway activity should both turn off the Wnt pathway (via a negative feedback loop) and turn on the Notch pathway (by binding to a negative regulator). The instability of Axin2 would later reverse the situation, leading to a continuous cycle.

The gradient idea arose because Wnt3a is made in the tail bud but can direct Axin2 expression throughout the PSM. High concentrations of Wnt3a near the tail bud prevent differentiation. But as the lengthening embryo puts more distance between the tail bud and the anterior, the level of Wnt3a in the anterior PSM drops. Below a certain threshold of Wnt3a, the Notch pathway can take over and direct somite development.

If this gradient was acting alone, the end result would be a steadily moving front of differentiation. But, as Herrmann points out, "the boundary position has to move back in a periodic manner. For that purpose you need the clock."

The clock operates only above the threshold level of Wnt3a—below this the cells get stuck in the "Notch on (Wnt off)" state. Above the threshold, all cells cycle together. But each time a new "Wnt on" cycle starts, the cells just below the threshold will not be able to join their more posterior neighbors, and for the first time there will be a boundary between "Wnt on" and "Notch (stuck) on." This boundary is the key: it defines the division between somites. The boundary only arises when the more posterior, above threshold, region cycles back up into a "Wnt on" state, so it is only laid down periodically. ■

Reference: Aulehla, A., et al. 2003. *Dev. Cell.* 4:395–406.

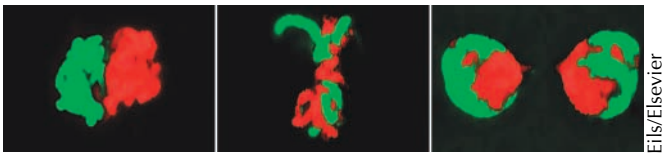
Chromosomes in the 'hood

It is almost unbearable (at least for scientists) to contemplate a complete lack of order. So, it comes as some relief that chromosomes may be positioned nonrandomly in the nucleus, thus giving rise to more frequent translocations between certain chromosomes.

The seeming chaos of mitosis led most researchers to believe that any such order would have to be reestablished after each division. But now Daniel Gerlich, Roland Eils (German Cancer Research Center, Heidelberg, Germany), Jan Ellenberg (EMBL, Heidelberg, Germany), and colleagues have found that positioning is maintained through mitosis by a timing mechanism.

Congressing chromosomes make a beeline for the metaphase plate, the group found, and thus preserve information about their relative position perpendicular to the spindle axis. But congression erases information about how far the chromosomes had to travel to reach the metaphase plate. Despite this, the group found that marked territories, chromosomes or centromeres reestablished their previous geographies after mitosis. (Conflicting conclusions were recently drawn by Walter et al. in these pages.)

Chromosomes reestablished their positions by initiating anaphase separation at different times. Chromosomes that started anaphase later ended up on the side of the nucleus closest to the daughter cell. This ordering was jumbled by a heterochromatin-binding drug, so Eils suggests that chromosomes with larger regions of pericentric heterochromatin may stick to each other for longer and thus initiate anaphase later. Such a mechanism should work through multiple cell divisions.



Eils/Elsevier

Marked chromosome areas are conserved through mitosis.

It is unlikely that the chromosomes are placed in locations with very different biochemistry: the placement is too rough, and most relevant proteins are in any case very mobile. So maybe the locations are merely a passive readout of kinetochore structure. Eils doesn't buy this argument. "I think Nature has invented this for a particular reason," he says, "but I don't yet know what reason." ■

References: Gerlich, D., et al. 2003. *Cell.* 10.1016/S0092867403001892. Walter, J., et al. 2003. *J. Cell Biol.* 160:685–697.